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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND PATENT INTERFERENCES**

Applicant: Sung-Yun KWON et al.
Title: METHOD OF ENHANCING
NEEDLELESS TRANSDERMAL
POWDERED DRUG DELIVERY
Appl. No.: 09/489,088
Filing Date: 01/21/2000
Examiner: Sung-Yun Kwon
Art Unit: 1615

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
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Sir:

This Appeal Brief is being filed with a check in the amount of \$500.00 covering the appeal and extension fees. If this amount is deemed insufficient, Appellants authorize charging any deficiency (as well as crediting any balance) to deposit account 19-0741.

This is an appeal from a final Office Action dated April 21, 2005, finally rejecting claims 1-18 and 20-32 under 35 U.S.C. § 103.

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I. REAL PARTY IN INTEREST

The real party in interest is the assignee, POWDERJECT RESEARCH LIMITED, 4 Robert Robinson Avenue, Oxford Science Park, Oxford, OX4 4GA, United Kingdom.

II. RELATED APPEALS AND INTERFERENCES

Neither the appellant, appellant's legal representative, or their assignee is aware of any related appeals or interferences that will affect directly or be affected directly by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1, 3, 5, 7, 11-18, and 20-32 are rejected, are on appeal, and are attached hereto as APPENDIX A. Claims 33-40 were withdrawn from consideration in response a Restriction Requirement dated March 30, 2001. Claims 2, 4, 6, 8-10, and 19 are canceled.

IV. STATUS OF AMENDMENTS

In response to a restriction requirement dated March 30, 2001, claims 1-32 were elected for prosecution on the merits and claims 33-40 were withdrawn from consideration. An RCE was filed on June 17, 2003 in which claim 19 was canceled and claim 1 was amended. In response to an Office Action dated April 21, 2005, claims 1 and 22 were amended and claims 2, 4, 6 and 8-10 were canceled.

V. SUMMARY OF THE CLAIMED INVENTION

The claimed invention provides a general method for administering a therapeutic agent to a predetermined area of the skin or mucosa of a vertebrate subject. Particles comprising the therapeutic agent are used. The method involves accelerating the particles into, across, or both into and across, the area of skin or mucosa. The particles are accelerated toward the skin or mucosa using a needleless syringe device. Next, a transdermal drug delivery device or occlusive dressing is topically positioned over the area of skin or mucosa.¹

¹ See, e.g., page 4, lines 6-14 of the specification.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The Examiner maintained a rejection of claims 1-18, and 20-32 under U.S.C. § 103(a) as allegedly being unpatentable over WO 98/29134 ('134) in view of U.S. Patent No. 5,630,796 ('796).¹

VII. ARGUMENTS

A. Rejection of Claims 1, 3, 5, 7, 11-18, and 20-32 Under 35 U.S.C. § 103(a) As Being Unpatentable Over WO 98/29134 (Eppstein) and U.S. Patent No. 5,630,796 (Bellhouse)

1. Examiner's Basis for the Rejection

Claims 1, 3, 5, 7, 11-18, and 20-32 stand rejected as allegedly obvious over WO 98/29134 ("WO '134") in view of United States Patent No. 5,630,796 ("Bellhouse"). Claim 1 of the present application recites that particles are accelerated into and/or across an area of skin or mucosa using a needleless syringe device. Subsequently, a transdermal delivery device or an occlusive dressing is topically positioned over the area of skin or mucosa. The particles contain the therapeutic agent.

The Examiner argues that the claimed invention would have been obvious over WO '134 in view of Bellhouse. The basis for the Examiner's position is the view that WO '134 teaches a method of enhancing the permeability of an active agent across a biological membrane, including skin and mucosa. In particular, the Examiner asserts that the method of WO '134 includes carrying out microporation of the membrane at a site of administration, followed by contacting the porated surface with a permeant (for example, a therapeutic agent) and a permeation enhancer. The Examiner then argues that WO '134 suggests forming pores using "any" non-invasive technique that does not require entry of a needle or invasive instruments into the skin or mucosa.

¹ Claims 1 and 22 were amended and claims 2, 4, 6 and 8-10 were canceled in Applicants Amendment after Final Rejection dated August 22, 2005. In the September 23, 2005 Advisory Action, the Examiner stated that the August 22, 2005 amendments would be entered. Therefore, this rejection applies to pending claims 1, 3, 5, 7, 11-18, and 20-32.

The Examiner acknowledges, however, that the primary reference, WO '134, does not teach or suggest the use of a needleless syringe to carry out the microporation. Nevertheless, the Examiner argues that it would have been obvious to use the needleless syringe described in Bellhouse to carry out the microporation step described by WO '134, and then to apply a topical patch containing an active agent as described in WO '134. On that basis, the Examiner argues that the claims at issue are obvious over WO '134 in view of Bellhouse. The Examiner asserts that one skilled in the art would have been motivated to combine these references because Bellhouse teaches that the needleless syringe method is a safe and quick method with less pain and no risk of infection. Finally, the Examiner asserts that a skilled artisan would have a reasonable expectation of successfully arriving at the claimed invention.

2. The combined teachings of Eppstein and Bellhouse do not Teach or Suggest Each and Every Limitation of the Claimed Invention

To establish a *prima facie* case of obviousness, there needs to be (1) some suggestion or motivation to modify the reference or to combine reference teachings, (2) a reasonable expectation of success, and (3) the prior art references, when combined, must teach or suggest all the limitations of the claimed invention. See MPEP §2143 (Aug. 2001). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants respectfully assert that the examiner has not met his burden.

The Examiner has failed to establish a *prima facie* case of obviousness because the combined teachings of Eppstein and Bellhouse do not teach or suggest each and every limitation of the claimed invention. Eppstein relates to a method where a surface is prepared by microporation for subsequent administration of a therapeutic agent. The method of Eppstein involves a two step process. Firstly, a biological membrane is prepared for the administration of a therapeutic agent by microporation, and secondly, the biological membrane which has been prepared in this way is contacted with a therapeutic agent and permeation enhancer. In contrast, amended claim 1 is directed to a method for enhancing the flux or improving the uptake of a therapeutic agent which is administered at the same time

that microporation takes place. In the claimed method, microporation is carried out at the same time as administration of the therapeutic agent. After the therapeutic agent has been administered, a transdermal delivery device or an occlusive dressing is positioned over the area of skin or mucosa which has been microporated and to which the therapeutic agent has (already) been administered.

The Examples in the specification illustrate the method of claim 1. Examples 1 and 2 demonstrate how the flux of insulin administered using a needleless syringe may be enhanced using an occlusive dressing, Example 3 demonstrates how the immunogenicity of a particulate HBV vaccine composition administered using a needleless syringe may be enhanced using an occlusive dressing, and Example 4 demonstrates how the uptake of calcitonin administered using a needleless syringe may be enhanced using an occlusive dressing. In each of these examples, the therapeutic agent is administered at the same time as microporation takes place and the application of an occlusive dressing takes place subsequent to administration of the therapeutic agent/microporation.

3. Eppstein Teaches Away from the Method of Claim 1

Eppstein arguably teaches away from the claimed invention because Eppstein teaches that microporation and the administration of a therapeutic agent are two separate steps that must be carried out sequentially.

Furthermore, the active agents that may be used in the method described by Eppstein include polypeptides and vaccines, optionally associated with a carrier. At page 14, line 25, to page 15, line 1, in particular, Eppstein refers to the use of carriers which comprise liposomes, lipid complexes, microparticles or polyethylene glycol compounds. Although Eppstein refers to microparticles, these microparticles are not particles that are intended for use with a needleless syringe. Instead, it appears that the microparticles disclosed by Eppstein have a lipid or polymer content. Such microparticles would likely not have the necessary strength to withstand the forces associated with delivery from a needleless syringe. That is to say, it does not seem that such microparticles would have sufficient structural integrity to withstand being fired from a needleless syringe and impacting skin or mucosal tissue at the very high

velocities that are necessarily associated with administration from a needleless syringe. This may be contrasted with the particles used in Example 1 of the present application. Example 1 describes the use of a particulate insulin formulation prepared using specific steps (lyophilisation, compression and milling) so as to ensure that the density of the particles is high enough for transdermal/transmucosal delivery at supersonic velocities. There is no suggestion in Eppstein that such steps should be taken. Therefore, it does not appear to be possible to use the particles in Eptstein with a needleless syringe. By teaching particles that are not intended for use with a needleless syringe, Eppstein teaches away from the claimed invention.

4. A Person of Ordinary Skill in the Art Would Not Have Been
Motivated to Combine the Teachings of Eppstein and Bellhouse

The Examiner states that a person of ordinary skill in the art would have been motivated to combine the teachings of Eppstein and Bellhouse to arrive at the claimed invention because Bellhouse teaches that the needleless method is "a safe and quick method with less pain and no risk of infection." Applicants respectfully disagree.

As discussed above, the Examiner has failed to establish a prima facie case of obvious because the combination of Eppstein and Bellhouse does not teach each and every limitation of the claimed invention. However, assuming arguendo that the combined teachings did teach each and every limitation of the claimed invention, a person of ordinary skill in the art would not have been motivated to combine the teachings of Eppstein and Bellhouse for the reasons discussed below.

(a) *Bellhouse teaches that the disclosed method should not
be combined with other methods*

Bellhouse teaches that the disclosed method should not be combined with other methods. For example, Applicants direct the Examiner's attention to the passage at column 1, lines 45 to 48 which explains that the needleless syringe is "useful for routine delivery of drugs, such as insulin..., and could be of use in mass immunisation programs, or for the

delivery of slow release drugs such as pain killers and contraceptives". Thus, Bellhouse makes it clear that the needleless syringe it describes is useful merely for the routine delivery of drugs and cannot reasonably be expected to be of use in a multi-step drug delivery technique, such as the method of claim 1, in which different drug delivery technologies are used to custom tailor drug delivery profiles. Therefore, Bellhouse would not have motivated a skilled artisan to combine its teachings with the teachings of Eppstein.

(b) Eppstein does not teach or suggest the use of particles administered via needleless syringe

Epstein does not teach or suggest the use of particles administered via a needleless syringe. The Examiner asserts that Eppstein suggests forming pores using "any" non-invasive technique that does not require entry of a needle into the skin or mucosa. The Examiner cites page 32, lines 10 to 11, to support the proposition. Applicants note that page 32, lines 10 to 11, defines the term "non-invasive" as "not requiring the entry of a needle, catheter, or other invasive instrument into the skin or mucous membrane." However, this portion of the Eppstein document does not teach or suggest that "any" non-invasive technique may be employed with the described method. In fact, Eppstein only discloses five methods of porating a biological membrane, none of which utilize the needleless injection technique taught by Bellhouse. Epstein does mention the use of a high pressure jet of fluid, but that disclosure occurs in the context of using the fluid itself to hydraulically puncture the biological membrane; this is of course different from using a fluid to propel a particle across the biological membrane as would be the case with a needleless syringe.

Moreover, although five types of poration are referred to in the description of WO '134, in reality, an even smaller number of specific types of poration is supported by the Examples of Eppstein, namely the use of a laser, thermal ablation, sonic energy and a combination of sonic energy with a chemical enhancer. Yet again, this emphasizes the fact that there is simply nothing in WO '134 which teaches or suggests the needleless injection technique taught in Bellhouse.

- (c) *The references fail to provide a teaching or suggestion that the needleless delivery method of Bellhouse would enhance the permeation of a subsequently administered therapeutic agent*

Finally, the Examiner's assertion that one skilled in the art would be motivated to combine the two references because Bellhouse teaches that the needleless method is a "safe [and] quick method with less pain and no risk of infection" is inapposite. Bellhouse does note that the "main advantages which flow from the invention include no needle and less pain, no risk of infection, delivery of drugs in natural solid form, quicker and safer to use than liquid drug, by syringe and needle and no sharps to dispose of." Bellhouse, col. 1, ll. 61-65. However, nothing in either of the references suggests that the needleless delivery method of Bellhouse would enhance the permeation of a subsequently administered therapeutic agent. Instead, Bellhouse merely discloses a method of delivering a therapeutic agent. The fact that the method is safe and quick, by itself, does not provide a motivation to combine the references. Accordingly, the Examiner's rationale does not provide any motivation to combine the Bellhouse method with a second method of delivering a therapeutic agent as disclosed in Eppstein.

Because the specification is not obvious over Eppstein in view of Bellhouse, Appellants courteously request that the Board reverse the Examiner's rejection of the claims.

VIII. CONCLUSION

The Board is respectfully requested to reconsider and reverse the outstanding rejection.

Respectfully submitted,

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APPENDIX A: CLAIMS ON APPEAL

1. A method for administering a therapeutic agent to a predetermined area of skin or mucosa of a vertebrate subject, said method comprising:

(a) accelerating particles into, across or both into and across the area of skin or mucosa, wherein the particles are accelerated toward the skin or mucosa using a needleless syringe device; and

(b) topically positioning a first transdermal drug delivery device or a first occlusive dressing over the area of skin or mucosa, wherein the particles comprise the therapeutic agent.

3. The method of claim 1, wherein the particles comprise a placebo.

5. The method of claim 1, wherein step (b) comprises topically positioning the first transdermal drug delivery device over the area of skin or mucosa.

7. The method of claim 1, wherein step (b) comprises topically positioning the first occlusive dressing over the area of skin or mucosa.

11. The method of claim 1, wherein the particles comprise an antigen.

12. The method of claim 1, wherein the particles comprise an adjuvant.

13. The method of claim 11, wherein the method further comprises a pretreatment step to administer an adjuvant to the area of skin or mucosa before step (a).

14. The method of claim 13, wherein the pretreatment step comprises topically positioning a second transdermal delivery device or a second occlusive dressing containing an adjuvant over the area of skin or mucosa.

15. The method of claim 11, wherein step (b) comprises topically positioning the first transdermal drug delivery device or the first occlusive dressing over the area of skin or

mucosa, and further wherein the first transdermal drug delivery device or first occlusive dressing contains an adjuvant.

16. The method of claim 1, wherein the particles comprise a permeation enhancing agent.

17. The method of claim 5, wherein the first transdermal delivery device is a passive transdermal delivery device.

18. The method of claim 5, wherein the first transdermal delivery device is an active transdermal delivery device.

20. The method of claim 1, wherein the particles are accelerated toward the skin or mucosal tissue at a velocity of about 200 to 3,000 m/sec.

21. The method of claim 1, wherein the particles have a diameter predominantly in the range of about 0.1 to 250 μm .

22. The method of claim 1, wherein the particles comprise a biologically active protein, a peptide, an oligosaccharide, a polysaccharide or a vaccine composition.

23. The method of claim 1, wherein step (a) provides for rapid delivery onset from the first transdermal delivery device.

24. The method of claim 5, wherein the particles and the first transdermal delivery device comprise the same therapeutic agent.

25. The method of claim 7, wherein the particles and the first occlusive dressing comprise the same therapeutic agent.

26. The method of claim 4, wherein the placebo comprises particles selected from the group consisting of a metal particle and a metal particle coated with a permeation enhancing agent.

27. The method of claim 9, wherein the placebo comprises particles selected from the group consisting of a metal particle and a metal particle coated with a permeation enhancing agent.

28. The method of claim 10, wherein the placebo comprises particles selected from the group consisting of a metal particle and a metal particle coated with a permeation enhancing agent.

29. The method of claim 6, wherein the particles comprise a permeation enhancing agent.

30. The method of claim 8, wherein the particles comprise a permeation enhancing agent.

31. The method of claim 1, further comprising before step (a), topically positioning over the area of skin or mucosa a second transdermal delivery device or a second occlusive dressing.

32. The method of claim 31, wherein the second transdermal delivery device or the second occlusive dressing contains a permeation enhancing agent.

33. (Withdrawn) A method for administering a therapeutic agent to a predetermined area of skin or mucosa of a vertebrate subject, said method comprising administering to said area of skin or mucosa (i) particles comprising a therapeutic agent, and (ii) placebo particles, wherein said particles are accelerated into, across or both into and across the area of skin or mucosa.

34. (Withdrawn) The method of claim 33, wherein the particles comprising the therapeutic agent and the particles comprising the placebo are administered simultaneously.

35. (Withdrawn) The method of claim 33, wherein the particles comprising the therapeutic agent and the placebo particles are accelerated toward the area of skin or muscosa using a needleless syringe device.

36. (Withdrawn) The method of claim 35, wherein the particles are accelerated toward the area of skin or mucosa at a velocity of about 200 to 3,000 m/sec.

37. (Withdrawn) The method of claim 33, wherein the particles comprising the therapeutic agent have a diameter predominantly in the range of about 0.1 to 250 μm .

38. (Withdrawn) The method of claim 37, wherein the placebo particles have a diameter predominantly in the range of about 10 μm to 50 μm .

39. (Withdrawn) The method of claim 33, wherein the placebo particles comprise about 1% to about 10% of the particles administered to the area of skin or mucosa.

40. (Withdrawn) The method of claim 33, wherein the placebo particles comprise a particle selected from the group consisting of a metal particle and a metal particle coated with a permeation enhancing agent.